A CONTROLLED RELEASE PHARMACEUTICAL COMPOSITION AND A PROCESS FOR PREPARING THE SAME

FIELD OF THE INVENTION

The present invention relates to antiretroviral pharmaceutical composition. The invention particularly relates to an antiretroviral pharmaceutical composition having a selective combination of a controlled release active formulation and an immediate release active formulation for once daily administration. The invention also relates to the process for manufacture of such once daily antiretroviral pharmaceutical composition.

BACKGROUND OF THE INVENTION

Acquired Immune Deficiency Syndrome (AIDS) which is caused by the human immunodeficiency virus (HIV) is one of the few diseases for which mankind is struggling to find a cure.

In the last several years many antiretroviral agents have been discovered that have since been used to treat AIDS. The drugs that are currently approved for anti-HIV therapy are broadly classified into three categories, namely:

1. Nucleoside Reverse Transcriptase Inhibitors (NRTI), which include lamivudine, zidovudine, didanosine, abacavir, stavudine, and zalcitabine.
2. Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI), which include nevirapine, efavirenz, and delavirdine.
3. Protease Inhibitors (PI), which include indinavir, ritonavir, nelfinavir, saquinavir and amprenavir.

For successful treatment of any disease caused by a microorganism the drug used in the therapy should eliminate the causative organism completely without allowing them to undergo mutation. Mutation may lead to resistant strains that can make treatment more difficult. This development of resistant strains is usually observed when a single agent or drugs belonging to a single category are solely used in the treatment. For most

diseases caused by microorganisms, it has been found that combining two or more drugs, preferably from different classes have resulted in a greater success rate.

Drugs for the treatment of highly active antiretroviral therapy were initially prescribed as a loose combination of two or three drugs. This was rationalised to fixed dose combinations to be administered twice daily. In our co-pending application number PCT/IN02/00110 we have described a formulation, which further reduced the pill burden to once a day. However to date there are no reports of once a day formulation comprising a three drug combination.

There are three known alternative regimens as follows:

1) 3 NRTIs
2) 2 NRTIs + 1 NNRTI
3) 2 NRTIs + 1 PI

Nucleoside-based reverse transcriptase inhibitors (NRTIs) were the first drugs to be given as antiretroviral agents, and they remain the backbone of therapy against HIV infection and acquired immuno deficiency syndrome (AIDS).

Although various therapy regimens have been tried as indicated above, it has been reported that drug combination comprising three NRTIs is not as effective as other combinations. The combination of two NRTIs, lamivudine and zidovudine which form the backbone of therapy with one NNRTI such as Nevaripine or Efavirenz is ideal. The serum half-life of Lamivudine is about 3 to 6 hours while that of Zidovudine is 1.1 hours. Nevaripine has a long half-life of more than 25 hours and is currently given as 200 mg twice daily. Efavirenz is approved for a dosing of 600 mg once daily.

We propose to use 400 mg Nevaripine to be given as a fixed dose combination with lamivudine and zidovudine once daily. In case of Efavirenz the amount of efavirenz or pharmaceutically acceptable derivative thereof is 600-800mg preferably.

Multi-drug therapy in case of antiretrovirals has the advantage that drugs have different mechanisms of action and act at different stages of the viral life cycle and they may

exhibit a synergistic effect on such use. However, this kind of therapy results in the patient having to take multiple pills several times a day and this is known to cause problems of compliance in following the therapy regimen. Several attempts have been made to reduce the pill burden in order to enhance patient compliance.

Lamivudine 150mg and zidovudine 300mg are NRTIs that are to be given twice daily. A fixed dose combination of lamivudine 150mg and zidovudine 300mg (COMBIVIR) has been developed which has reduced the pill load for this combination to two. Similarly, a three drug fixed dose combination of lamivudine 150 mg, zidovudine 300 mg and abacavir 300 mg (TRIZIVIR) has also been developed. However, there are reports of toxicity related to abacavir. Further, the frequency of dosing for both two and three drug combination is still twice daily.

United States Patent No. 6,113,920 discloses a pharmaceutical composition comprising two active pharmaceutical ingredients namely lamivudine and zidovudine and a pharmaceutically acceptable glidant ingredient, selected from a group of colloidal silicon dioxide, microcrystalline cellulose, metallic stearates, calcium carbonate and combinations thereof, in the form of a film coated tablet. The composition contains lamivudine in an amount from 15 to 1500 mg per tablet and zidovudine in an amount from 30 to 1000 mg per tablet. This combination is given twice daily.

United States Patent No. 4,917,900 discloses a pharmaceutical formulation for oral administration in which discrete units comprising zidovudine are provided with a controlled release coating consisting of alkyl esters of acrylic and methacrylic acids and ethylcellulose in a weight ratio of 1:3 to 3:1. These spheroids contain at least 80% of zidovudine and microcrystalline cellulose and mannitol as the core-forming agent.

As discussed above, while a two drug combination product may reduce the pill burden to half, it still has to be given twice daily and when coupled with a third drug, the pill burden is substantially increased.

OBJECTS OF THE INVENTION

It is thus the basic object of the present invention to provide for a three-drug antiretroviral pharmaceutical composition, which would reduce the pill load and frequency of drug administration thereby favouring patient compliance and effective treatment.

Another object is to provide a fixed dose combination of lamivudine, zidovudine and atleast one NNRTI drug suitable for once daily administration, which would reduce the pill burden to one and the frequency to once daily.

Yet further object of the present invention is directed to the development of a three drug fixed dose combination comprising essentially the antiretroviral drugs lamivudine, zidovudine, and at least one NNRTI drug preferably selected from nevirapine and efavirenz suitable for once daily dosing wherein lamivudine and zidovudine would have a controlled release while nevirapine/ efavirenz will be immediately released.

Yet another object of the present invention is related to a method of increasing the in vivo half life of Lamivudine and Zidovudine while not affecting the half life of Nevirapine or Efavirenz and thus reducing the pill burden in a patient suffering from HIV infection and / or Acquired Immunodefficiency Syndrome by administering a three drug antiretroviral composition which comprises of Lamivudine and Zidovudine as a controlled release component and nevirapine or efavirenz as an immediate release component

Yet further object is directed to provide a process for preparing an antiretroviral pharmaceutical composition as above which would reduce the pill load and frequency of drug administration thereby favouring patient compliance and effective treatment.

SUMMARY OF THE INVENTION

Thus according to the present invention there is provided an antiretroviral pharmaceutical composition comprising a selective combination of

i. a controlled release formulation comprising :

a. lamivudine or a pharmaceutically acceptable derivative thereof,
b. zidovudine or a pharmaceutically acceptable derivative thereof, and
c. a mixture of hydrophilic polymers, said polymers being selected from the group consisting of cellulose ethers, polyuronic acids and pharmaceutically acceptable gums or mixtures thereof and
d. a pharmaceutically acceptable calcium salt.

ii. an immediate release formulation comprising at least one selective non-nucleoside reverse transcriptase inhibitors (NNRTI) drug or a pharmaceutically acceptable derivative thereof along with pharmaceutically acceptable excipients.

In accordance with another aspect of the present invention there is provided a process for the preparation of a pharmaceutical composition comprising

(i) mixing together active ingredients selected from amongst lamivudine, zidovudine or pharmaceutically acceptable derivatives thereof or mixtures thereof with hydrophilic polymers selected from amongst cellulose ethers, polyuronic acids, pharmaceutically acceptable gums or mixtures thereof, and with a pharmaceutically acceptable calcium salt, optionally a diluent and a lubricant to provide a controlled release formulation
(ii) providing an immediate release formulation obtained of at least one NNRTI or pharmaceutically acceptable derivatives thereof blended with pharmaceutically acceptable excipients and
(iii) obtaining a composition therefrom by compressing the resulting blends into bilayered tablets, or by applying the said immediate release formulation as an outer coat over the core of the said controlled release formulation

DETAILED DESCRIPTION OF THE INVENTION

The pharmaceutical composition is preferably in the form of a bilayered tablet with the controlled release comprising one layer and the immediate release comprising the second layer. Alternatively the controlled release component may be in the form of a core and the second immediate release layer may be coated on top of the core.

The controlled release layer of the pharmaceutical composition comprises lamivudine and zidovudine or their pharmaceutically acceptable derivatives along with a mixture of hydrophilic polymers selected from the group consisting of cellulose ethers, polyuronic acids, pharmaceutically acceptable gums, or mixtures thereof.

In addition, this layer also comprises a pharmaceutically acceptable calcium salt and optionally one or more water-soluble or water dispersible pharmaceutically acceptable excipients.

The cellulose ether used in accordance with the present invention is selected from amongst those commonly known in the art such as hydroxypropyl cellulose, hydoxypropyl methylcellulose, carboxy methylcellulose, sodium carboxymethylcellulose, ethyl cellulose, methyl cellulose, hydroxy ethyl cellulose and the like. It is present in an amount from about 2% to about 12% by weight of the controlled release layer and preferably in an amount from about 3% to about 8% by weight of the controlled release layer.

The polyuronic acid used in accordance with the present invention is selected from amongst alginic acid, sodium alginate, calcium alginate, sodium calcium alginate, potassium alginate, ammonium alginate, magnesium alginate and the like. It is present in an amount from about 0.5% to about 10% by weight of the controlled release layer and preferably in an amount from about 1% to about 6% by weight of the controlled release layer.

The pharmaceutically acceptable gum used in the composition of the invention is selected from amongst those commonly known in the art such as guar gum, xanthan gum, gum karaya, tragacanth gum, gum acacia and the like. It is present in an amount from about 0.1% to about 10% by weight of the controlled release layer and preferably in an amount from about 0.5% to about 6% by weight of the controlled release layer.

Calcium salts when used along with certain polymers, especially the alginates, have been known to stabilize the matrix. In accordance with this, in a preferred embodiment,

the said controlled release layer of the composition also contains a pharmaceutically acceptable calcium salt.

The calcium salt is selected from the group consisting of calcium sulphate, calcium phosphate, calcium carbonate and calcium chloride. It is present in an amount from about 0.1% to about 2.5% by weight of the controlled release layer preferably from about 0.1% to about 2% by weight of the controlled release layer.

The controlled release layer of the composition may further contain one or more pharmaceutically acceptable other excipients selected from amongst water-soluble and/or water dispersible diluents and lubricants.

The water dispersible or water soluble diluent selected from amongst microcrystalline cellulose, dicalcium phosphate, calcium carbonate, lactose, powdered cellulose, starch, mannitol and the like. They are present from about 1% to about 28% by weight of the controlled release layer.

When the diluent is microcrystalline cellulose,it is present in an amount from about 5% to about 20% by weight of the controlled release layer.

When the diluent is dicalcium phosphate, it is present in an amount from about 1% to about 5% by weight of the controlled release layer.

The immediate release layer comprises at least one NNRTI selected from amongst nevirapine and efavirenz or their pharmaceutically acceptable derivatives

The immediate release layer may further comprise pharmaceutically acceptable excipients selected from the group consisting of diluents, binders, disintegrants, lubricants, coloring agents and the like.

The diluent is selected from amongst microcrystalline cellulose, dicalcium phosphate, calcium carbonate, lactose, powdered cellulose, starch, mannitol and the like. The

diluent is present in an amount from about 2% to about 15% by weight of the immediate release layer.

The binder is selected from amongst carboxymethylcellulose sodium, povidone, pregelatinised starch, gelatin, and the like. The binder is present in an amount from about 1% to about 10% by weight of the immediate release layer.

The disintegrant is selected from amongst crospovidone, sodium starch glycolate, pregelatinised starch, carboxymethylcellulose sodium, croscarmellose sodium, starch and the like. It is present in an amount from about 0.5% to about 15% by weight of the immediate release layer.

Each layer may also contain lubricants selected from amongst those commonly known in the art such as magnesium stearate, calcium stearate, stearic acid, silicon dioxide, talc and the like. It is present in an amount from about 0.1% to about 3% by weight of each layer.

The pharmaceutical compositions according to the invention may be prepared by procedures well known to those skilled in the art. According to a convenient method for the preparation of the granular blend for each layer, all the active ingredients along with the necessary excipients are mixed together and then compacted. The compacted mass is then comminuted to obtain the granules. Alternatively, the granules may also be prepared by the process of wet granulation using a suitable granulating agent.

The final granular blend of the two layers are either compressed into bilayered tablets on a compression machine suitable for such purpose or the controlled release layer may be present as a core and the immediate release layer is present as a coat around the core. The tablets so obtained may be further coated using a water-soluble polymer.

The above-mentioned process results in a pharmaceutical composition that contains three antiretroviral agents in one tablet suitable for once daily administration. The effective therapeutic dose of the active that can be administered include a combination

of 300 mg of lamivudine, 600 mg of zidovudine and 400 mg of nevirapine/ 600 mg of efavirenz.

The composition of the invention and its advantages are explained hereunder in greater detail in relation to non-limiting examples hereunder:

Example 1

Ingredients	**Weight (mg/tab)**
Controlled Release Layer	
Lamivudine	300.0
Zidovudine	600.0
Microcrystalline Cellulose	187.0
Hydroxypropyl methylcellulose	62.5
Sodium alginate	31.25
Guar gum	12.5
Calcium sulphate	3.75
Dicalcium phosphate	40.0
Magnesium Stearate	13.0
Immediate Release Layer	
Nevirapine	400.0
Powdered Cellulose	52.5
Povidone K30	20.0
Sodium starch glycolate	15.0
Magnesium stearate	3.75
Sodium starch glycolate	5.0
Colloidal silicon dioxide	2.5
Magnesium stearate	1.25

Controlled release layer blend: Lamivudine, zidovudine, hydrophilic polymers, calcium sulphate, dicalcium phosphate, and microcrystalline cellulose were screened through 30 no. mesh and mixed with magnesium stearate. The blend was compacted and the slugs obtained were milled to form granules. The sized granules were blended with fines and lubricated.

Immediate release layer blend: Nevirapine, cellulose, povidone and a first portion of sodium starch glycolate were screened through 40 no. mesh and mixed with magnesium stearate. The blend was compacted and the slugs obtained were milled to form granules. The granules were mixed with a second portion of sodium starch glycolate, colloidal silicon dioxide and lubricated.

Bilayered tablets: Both the above blends were compressed into bilayered tablets using a bilayered tablet compression machine.

Drug Release: The tablets were tested for release of all three actives using USP Type 1 Dissolution apparatus at an RPM of 100 and with 900ml of 0.1N HCL for the first 2 hrs and pH 6.8 Phosphate buffer afterwards.

Time	**% Drug released**		
	Lamivudine	Zidovudine	Nevirapine
1hr	29.1	17.1	87.1
2hrs	42.7	25.9	
4hrs	55.5	42.3	
8hrs	70.4	67.6	
10hrs	79.4	80.1	
12hrs	85.3	88.2	

Example 2

Ingredients	Weight (mg/tab)
Controlled Release Layer	
Lamivudine	300.0
Zidovudine	600.0
Microcrystalline Cellulose	187.0
Hydroxypropyl methylcellulose	62.5
Sodium alginate	31.25
Guar gum	12.5
Calcium sulphate	3.75
Dicalcium phosphate	40.0
Magnesium Stearate	13.0
Immediate Release Layer	
Nevirapine	400.0
Powdered Cellulose	35.0
Povidone K30	20.0
Crospovidone	15.0
Sodium starch glycolate	20.0
Sunset Yellow FCF	2.5
Magnesium stearate	5.0
Colloidal silicon dioxide	2.5

The manufacturing procedure of Example 1 was followed.

The release of the drugs was obtained as follows:

Time	% Drug released		
	Lamivudine	Zidovudine	Nevirapine
1hr	-	-	94.2
2hrs	47.0	26.8	
4hrs	61.7	43.0	
8hrs	71.3	64.8	
10hrs	79.1	75.4	
12hrs	86.6	76.7	
14hrs	90.5	89.2	

Example 3

Ingredients	Weight (mg/tab)
Controlled Release layer	
Lamivudine	300.0
Zidovudine	600.0
Microcrystalline Cellulose	187.0
Hydroxypropyl methylcellulose	62.5
Sodium alginate	31.25
Guar gum	12.5
Calcium sulphate	3.75
Dicalcium phosphate	40.0
Magnesium Stearate	13.0
Immediate Release layer	
Nevirapine	400.0
Powdered Cellulose	42.5
Povidone K30	10.0.
Crospovidone	20.0
Sodium starch glycolate	15.0
Magnesium stearate	3.75
Sodium starch glycolate	5.0

Colloidal silicon dioxide	2.5
Magnesium stearate	1.25

The manufacturing procedure of Example 1 was followed

The release obtained of the drugs is as follows:

Time	**% Drug released**		
	Lamivudine	Zidovudine	Nevirapine
1hr	33.8	21.3	97.1
2hrs	50.5	31.0	
4hrs	67.8	49.5	
8hrs	79.2	74.0	
10hrs	86.2	83.7	
12hrs	90.6	90.1	

Example 4

Ingredients	**Weight (mg/tab)**
Core	
Lamivudine	300.0
Zidovudine	600.0
Microcrystalline Cellulose	187.0
Hydroxypropyl methylcellulose	62.5
Sodium alginate	31.25
Guar gum	12.5
Calcium sulphate	3.75
Dicalcium phosphate	40.0
Magnesium Stearate	13.0
Coat	
Nevirapine	400.0

Powdered Cellulose	32.5
Povidone K30	20.0
Crospovidone	20.0
Sodium starch glycolate	15.0
Magnesium stearate	3.75
Sodium starch glycolate	5.0
Colloidal silicon dioxide	2.5
Magnesium stearate	1.25
Sunset Yellow FCF	2.5

Core: Lamivudine, zidovudine, hydrophilic polymers, calcium sulphate, dicalcium phosphate, and microcrystalline cellulose were screened through 30 no. mesh and mixed with magnesium stearate. The blend was compacted and the slugs obtained were milled to form granules. The sized granules were blended with fines, lubricated and compressed into a tablet.

Coat: Nevirapine, cellulose, povidone and a first portion of sodium starch glycollate were screened through 40 no. mesh and mixed with magnesium stearate. The blend was compacted and the slugs obtained were milled to form granules. The granules were mixed with a second portion of sodium starch glycolate, colloidal silicon dioxide, lubricated and compression coated over the core tablet.

The release obtained of the drugs is as follows:

Time	**% Drug released**		
	Lamivudine	Zidovudine	Nevirapine
1hr	37.4	22.8	80.8
2hrs	54.1	32.1	
4hrs	66.5	47.5	
8hrs	82.5	76.8	
10hrs	92	87.3	
12hrs	97.3	93.7	

A single dose fed study was conducted using the tablets of Example 1 against a commercially available immediate release combination of the three drugs. The results of the study are tabulated in Table 1.

	Test: Lamivudine 300 mg (as ER) + Zidovudine 600mg (as ER) + Nevirapine 400mg (OD) tablets			Reference: Lamivudine 150 mg +Zidovudine 300 mg + Nevirapine 200 mg (IR/BD) tablets		
	Lamivudine	Zidovudine	Nevirapine	Lamivudine	Zidovudine	Nevirapine
C_{max} (mcg/ml)	1.79	1.54	5.17	1.51	1.49	2.88
$AUC_{(0-t)}$ (mcg.hr/ml)	12.18	7.45	36.37	5.84	3.12	18.55
$t_{1/2}$ (hr)	5.67	2.74	29.34	2.98	0.72	17.82

The results indicate that the composition of the present invention achieves a C_{max} of Lamivudine and Zidovudine, which is equivalent to that obtained when the same drugs are administered in immediate release form. However, the invention also succeeds in increasing the AUC_{0-t} values and the half lives of all the drugs in vivo.

It is thus apparent from the above exemplary illustrations that the pharmaceutical composition of the invention serves as a three-drug antiretroviral combination for once daily dosage for a combination treatment especially of NRTIs and NNRTIs. The once daily dosage form of the invention is simple and cost-effective and would serve in reducing the pill burden and frequency of administration and favour patient compliance with the desired drug regime for effective treatment.